Advanced Imaging in Glioma Treatment

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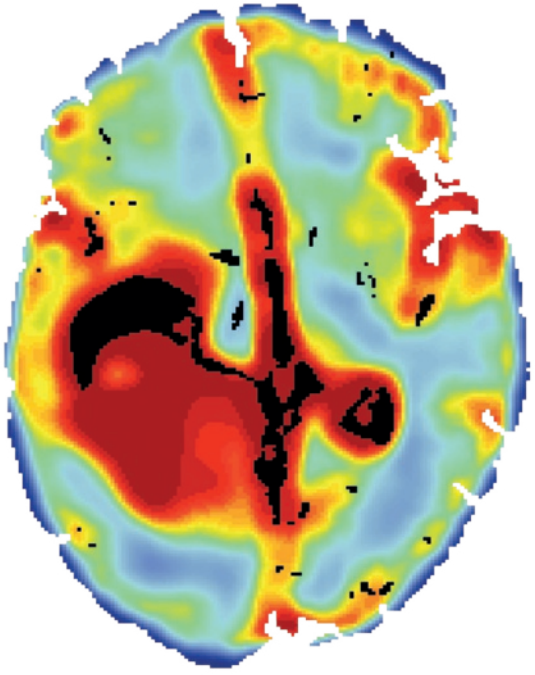
Appendices



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II. Summary

This thesis set out to answer the following question: “Which MRI sequence, PET tracer, or combination of MRI sequence(s) and/or PET tracer(s) is the most accurate for the detection of diffuse glioma infiltration?”.

Chapter 1 provides a general introduction, as well as the aim and outline of this thesis. After a description of the biological and clinical background of diffuse gliomas, we address the difficulty of the detection of diffuse glioma infiltration and the available imaging techniques for the detection of this infiltration. The aims of this thesis are: to discuss the current literature concerning imaging for the detection of diffuse glioma infiltration; to develop quantitative [^{18}F]FET PET parametric maps; to compare the accuracy of different MRI sequences, PET tracers and combinations of MRI sequence(s) and/or PET tracer(s) for the detection of diffuse glioma infiltration; and to quantify such infiltration using histological, molecular and imaging techniques.

In **chapter 2** we systematically review the current literature on the diagnostic accuracy of imaging techniques for the detection of diffuse glioma infiltration. This meta-analysis on 61 studies, describing 3,532 samples in 1,309 patients, has several findings. First, the reporting quality of the studies is suboptimal. Second, the diagnostic accuracy for the detection of diffuse glioma infiltration of standard MRI used in daily practice is better for low-grade than high-grade glioma. Third, the diagnostic accuracy for the detection of diffuse glioma infiltration of standard MRI in high-grade gliomas is lower than MR spectroscopy and PET. Finally, samples without tumor presence from regions without imaging abnormalities (true negative samples) are underrepresented. Based on these findings, we conclude that a prospective study with direct comparison of imaging techniques including true negative samples is needed.

In **chapter 3** we discuss the literature on current available imaging techniques for the guidance of diffuse glioma resection and the localization of brain functions and white matter tracts. We conclude that, although multiple imaging techniques are available, studies directly comparing the guidance of diffuse glioma resection by different imaging techniques are sparse. The results of these few studies suggest that the use of other imaging techniques than the current standard MRI could result in improved survival for

patients. Another conclusion of this review is that direct cortical stimulation remains the gold standard for the localization of important brain functions and white-matter tracts. Imaging techniques, however, are indispensable for surgical planning, including the choice of awake versus non-awake surgery.

Chapter 4 comprises a study of the accuracy of an in-house developed stereotactic drilling technique for diagnostic biopsies and stereo-electroencephalography depth electrode implantation. We included seven patients with 89 depth electrodes implanted and compared the pre-operative neuronavigation planning with the actual position on post-operative CT. The difference between planning and actual position was 3.5mm. Therefore, we conclude that our stereotactic drilling technique is suitable for diagnostic biopsies.

Chapter 5 describes the study protocol for a monocenter prospective diagnostic accuracy study for the detection of diffuse glioma infiltration. Inclusion encompasses adult patients with a newly diagnosed, diffuse infiltrative glioma undergoing resective glioma surgery. Advanced neuroimaging is added to the standard preoperative MRI, and both are used to plan serial neuronavigated biopsies in and around the glioma boundaries. Biopsies are obtained immediately preceding resective surgery and provide histopathological and molecular characteristics of the regions of interest, enabling comparison with quantitative measurements in the imaging modalities at the same biopsy sites.

Chapter 6 examines different tracer kinetic models for the quantification of [^{18}F]FET kinetics in seven patients. The purpose of this study is to identify the optimal model using full plasma input data, as well as to identify the optimal simplified model that does not require arterial or venous blood sampling. The reversible two-tissue compartment model was the optimal tracer kinetic model and showed a strong correlation with the 60–90 min tumor-to-blood ratio, which was therefore identified as the optimal simplified model. There was also a significant, although moderate, correlation between [^{18}F]FET kinetics and cerebral blood flow, determined by [^{15}O]H_2O PET. We conclude that the optimal simplified method is accurate enough to replace the full plasma input method.

Chapter 7 compares multiple parametric maps of [^{18}F]FET kinetics as well as tumor-to-brain ratio maps from different [^{18}F]FET PET time intervals in seven patients. In order to assess the accuracy of the parametric maps, the mean value of the tumor volume was determined with the optimal model from chapter 6 and compared with the mean

value of the tumor volume of the different parametric maps. The quality of each image was assessed as the level of noise, with lower levels of noise representing higher image quality. The parametric maps based on the basis function method provided the best accuracy, while the parametric map based on the Logan method displayed the lowest level of noise. Tumor-to-normal ratio maps provided better accuracy and lower noise if later interval times were used.

Chapter 8 consists of a study directly comparing [^{18}F]FET and [^{11}C]choline PET for the detection of diffuse glioma infiltration in 74 samples from eight patients. The diagnostic accuracy of both the standardized uptake value (SUV) and the tumor-to-brain ratio (TBR) maps of [^{11}C]choline and different time intervals of [^{18}F]FET were assessed. For [^{18}F]FET, the diagnostic accuracy of the TBR was higher than that of the SUV for intervals 40–60 min and 60–90min. For [^{11}C]choline, there was no difference in diagnostic accuracy between the SUV and the TBR, however, there was a significant difference between tumor and normal samples SUV, but not TBR. The diagnostic accuracy of [^{18}F]FET TBR 60-90 min was higher than that of [^{11}C]choline SUV 20-40 min. We conclude that [^{18}F] FET PET is more accurate than [^{11}C]choline PET for detecting diffuse glioma infiltration.

Chapter 9 presents the results of the direct comparison of diagnostic accuracy of multiple MRI sequences, PET tracers and combinations of MRI sequence(s) and/or PET tracer(s) for the detection of diffuse glioma infiltration in 174 samples from 20 patients. In enhancing gliomas, the combination of ADC with [^{18}F]FET PET detected diffuse glioma infiltration better than T1G MRI and better than [^{18}F]FET PET. In non-enhancing gliomas, no imaging combination detected diffuse glioma infiltration significantly better than standard MRI. FLAIR-weighted MRI was more accurate than [^{18}F]FET PET in non-enhancing glioma. We constructed a probability map of tumor presence based on the combination of ADC with [^{18}F]FET PET, with each voxel representing the probability of tumor presence, ranging from 0 to 100%. We conclude that combining ADC and [^{18}F] FET PET detects diffuse glioma infiltration better than standard MRI and [^{18}F]FET PET in enhancing gliomas, potentially enabling better local therapy.

Chapter 10 quantifies diffuse glioma infiltration using different techniques and assesses intratumoral epigenetic heterogeneity in 133 samples of 16 patients. Diffuse glioma infiltration was quantified as tumor purity using (epi)genetic, histological and radiological metrics. An epigenetic tumor purity metric (PAMES) correlated best with all other metrics. Also, tumor purity demonstrated high intrapatient spatial variation.

Intratumoral epigenetic heterogeneity was analyzed at molecular epigenetic classification level and compared with intratumoral variation in tumor purity. We conclude that apparent spatial heterogeneity in molecular epigenetic classification can generally be explained by variation in tumor purity and generally does not reflect biological variation. Genome-wide intratumoral epigenetic heterogeneity was also analyzed and confirmed the findings at molecular epigenetic classification level.

Finally, in **Chapter 11**, we present the general discussion of this thesis including: the current standard radiological imaging for the detection of diffuse glioma infiltration; imaging combinations for the detection of diffuse glioma infiltration; and quantification of diffuse glioma infiltration. Furthermore, we discuss the future perspectives of a new standard imaging protocol for diffuse glioma and local treatment beyond current standard MRI abnormalities. Finally, suggestions are made for future research.

III. Nederlandse samenvatting

(SUMMARY IN DUTCH)

Diffuse gliomen zijn de meest voorkomende hersentumoren. Ze ontstaan uit de (voorlopers van) gliacellen die als functie hebben de zenuwcellen (neuronen) in de hersenen te ondersteunen. De mate van kwaadaardigheid wordt uitgedrukt in een graderingssysteem van de Wereldgezondheidsorganisatie, waarbij graad I de minst en graad IV de meest kwaadaardige tumoren zijn. Diffuse gliomen zijn er in graad II, III en IV, waarbij graad IV glioblastoom wordt genoemd. Per jaar krijgen ongeveer 1100 mensen in Nederland een diffuus glioom, hiervan betreft het in circa 60% van de patiënten een glioblastoom.

De behandeling van diffuse gliomen bestaat uit een operatie en - afhankelijk van de graad, leeftijd en conditie van patiënt – bestraling en chemotherapie. Het doel van de operatie is om zo veel mogelijk tumorweefsel te verwijderen zonder ernstige neurologische uitval bij de patiënt te veroorzaken. De 10-jaars overleving is ongeveer 17%, hierdoor staan diffuse gliomen in de top vijf van meest dodelijke kankersoorten. Eén van de redenen dat diffuse gliomen zo moeilijk te behandelen zijn is hun neiging om het omliggende gezonde hersenweefsel wijdverspreid te infiltreren. Hierdoor is het lastig om tijdens een operatie onderscheid te maken tussen de tumor en normaal hersenweefsel. Om te helpen dit onderscheid te maken wordt er gebruik gemaakt van beeldvorming. De meest gebruikte techniek is beeldvorming met behulp van magnetische resonantie (MRI). MRI beelden kunnen op verschillende manieren verkregen worden, zogenaamde sequenties. De T2-, FLAIR- en T1 met contrast-gewogen sequenties zijn de huidige standaard voor het afbeelden van de infiltratie van een diffuus glioom. Er zijn ook andere MRI-sequenties en andere beeldvormende technieken, zoals bijvoorbeeld positronemissietomografie (PET) waarvoor meerdere radioactief gemerkte stoffen (tracers) bestaan, beschikbaar voor het afbeelden van deze tumorinfiltratie. Het is echter nog onvoldoende duidelijk of deze alternatieven beter zijn dan de huidige standaard.

Dit proefschrift heeft als doel het beantwoorden van de vraag: “Welke MRI sequentie, PET-tracer, of combinatie van MRI-sequentie(s) en/of PET-tracer(s), is het meest nauwkeurig voor het afbeelden van diffuusglioom-infiltratie?”.

Hoofdstuk 1 betreft een algemene introductie en een korte beschrijving van het doel en de opzet van dit proefschrift. In de algemene discussie wordt eerst de biologische en klinische achtergrond van diffuse gliomen beschreven. Vervolgens komt de moeilijkheid van het detecteren van de infiltratie van diffuse gliomen aan de orde. De doelen van dit proefschrift zijn: bediscussiëren van de huidige literatuur omtrent beeldvorming voor het detecteren van de infiltratie van diffuus gliomen; ontwikkelen van PET beelden die gebaseerd zijn op metingen van de verdeling van de tracer [^{18}F]FET, zogenaamde parametrische beelden; het vergelijken van de nauwkeurigheid van verschillende MRI-sequenties, PET-tracers, of combinatie van MRI-sequentie(s) en/of PET-tracer(s), voor het detecteren van de infiltratie van diffuse gliomen; en het kwantificeren van de diffuus glioom infiltratie met behulp van histologische, moleculaire en beeldvormende technieken.

Hoofdstuk 2 bevat een systematische review van de literatuur over de diagnostische nauwkeurigheid van beeldvormende technieken voor het detecteren van diffuusglioom-infiltratie. Deze meta-analyse over 61 studies met 3,532 biopten in 1,309 patiënten leidde tot een aantal bevindingen. Ten eerste was de kwaliteit van rapporteren van de studies suboptimaal. Ten tweede, de diagnostische nauwkeurigheid voor het detecteren van diffuusglioom-infiltratie van standaard MRI, welke gebruikt wordt in de dagelijkse praktijk, is beter voor laaggradige dan hooggradige gliomen. Ten derde, de diagnostische nauwkeurigheid voor het detecteren van diffuusglioom-infiltratie van standaard MRI in hooggradige gliomen was minder dan die van magnetische resonantie spectroscopie en PET. Tot slot waren biopten zonder tumor uit gebieden zonder afwijkingen op de beeldvorming (echt negatieve biopten) ondervertegenwoordigd. Gebaseerd op deze bevindingen concluderen wij dat er een noodzaak is tot een prospectieve studie met directe vergelijking van beeldvormende technieken waarbij ook echt negatieve biopten worden verkregen.

In **hoofdstuk 3** bediscussiëren wij de literatuur omtrent de huidige beschikbare beeldvormende technieken voor het begeleiden van de resectie van diffuse gliomen en het lokaliseren van hersenfuncties en wittestofbanen. We concluderen dat er, ondanks de beschikbaarheid van meerdere beeldvormende technieken, weinig studies zijn die diffuusglioom-resecties op basis van verschillende beeldvormende technieken direct vergelijken. De resultaten van deze spaarzame studies suggereren dat het gebruik van andere beeldvormende technieken dan de huidige standaard MRI mogelijk zou kunnen leiden tot een verbeterde overleving van patiënten. Een andere conclusie is dat

directe corticale stimulatie de goudstandaard blijft voor het lokaliseren van belangrijke hersenfuncties en wittestofbanen. Beeldvormende technieken zijn echter onmisbaar voor de chirurgische planning, inclusief de keuze voor een wakkere, versus niet-wakkere, operatie.

Hoofdstuk 4 bevat een studie naar de nauwkeurigheid van een stereotactische boortechniek, welke lokaal is ontwikkeld, voor diagnostische biopten en het inbrengen van stereo-electroencefalografische diepte-elektroden. We includeerden zeven patiënten met 89 ingebrachte diepte-elektroden en vergeleken de preoperatieve neuro-navigatieplanning met de uiteindelijke positie op de CT. Het verschil tussen de planning en uiteindelijke positie was 3.5 mm. Daarom concluderen we dat onze stereotactische boortechniek geschikt is voor diagnostische biopten.

Hoofdstuk 5 beschrijft het studieprotocol van een monocentrische prospectieve diagnostische nauwkeurigheid studie voor de detectie van diffuusglioom-infiltratie. Inclusie zal bestaan uit volwassen patiënten met een nieuwgediagnosticeerd diffuus glioom die een chirurgische resectie ondergaan. Geavanceerde beeldvormende technieken worden toegevoegd aan het standaard MRI-protocol. Beide worden gebruikt voor het plannen van seriële neurogenavigeerde biopten in, en rondom, de grenzen van het glioom. Biopten worden direct voorafgaande aan de resectie verkregen en gebruikt om de histopathologische en moleculaire kenmerken te bepalen. Dit maakt vergelijking met kwantitatieve metingen van de beeldvormende technieken van het biopsie gebied mogelijk.

In **hoofdstuk 6** onderzoeken we verschillende kinetische modellen voor tracers om de [^{18}F]FET-kinetiek te kwantificeren in zeven patiënten. Het doel van deze studie was het identificeren van het optimale volledige model met behulp van de data van de bloedafnames, alsmede het identificeren van het optimale versimpelde model, welke bloedafnames overbodig maakt. Het reversibele twee-weefsel compartimentmodel was het optimale volledige tracerkinetische model en liet een sterke correlatie zien met de 60-90 min tumor-brein ratio, waardoor deze ratio als het optimale versimpelde model werd geïdentificeerd. Ook vonden we een matige maar significante correlatie tussen de [^{18}F]FET-kinetiek en cerebrale bloedstroom, zoals gemeten door middel van [^{15}O]H_2O PET. We concluderen dat de optimale versimpelde methode nauwkeurig genoeg is om de optimale volledige methode te vervangen.

In **hoofdstuk 7** vergelijken we in zeven patiënten meerdere [^{18}F]FET PET parametrische beelden, alsmede tumor-brein ratio (TBR) beelden van verschillende [^{18}F]FET PET intervallen. Om de nauwkeurigheid van de parametrische beelden te bepalen werd de gemiddelde waarde van het tumorvolume bepaald met behulp van de optimaal volledige methode uit hoofdstuk 6. Deze gemiddelde waarde werd vervolgens vergeleken met de gemiddelde waarde van het tumorvolume van de verschillende parametrische beelden. De kwaliteit van de beelden werd bepaald door de ruis te bepalen, waarbij minder ruis een betere beeldkwaliteit geeft. De parametrische beelden op basis van de basis functie methode waren het meest nauwkeurig. De parametrische beelden op basis van de Logan grafische analyse hadden de minste ruis. De nauwkeurigheid en ruis van de TBR-beelden waren beter voor de latere tijdsintervallen.

Hoofdstuk 8 bevat een studie met een directe vergelijking van [^{18}F]FET en [^{11}C]choline PET voor de detectie van diffuusglioom-infiltratie in 74 biopten van acht patiënten. De nauwkeurigheid van zowel de gestandaardiseerde opname waarde (SUV) als de TBR van [^{11}C]choline en de verschillende tijdsintervallen van [^{18}F]FET werden bepaald. Voor [^{18}F]FET was de diagnostische nauwkeurigheid voor de detectie van diffuusglioom-infiltratie van de TBR hoger dan van de SUV voor de tijdsintervallen 40–60min en 60–90min. Voor [^{11}C]choline was er geen verschil in de diagnostische nauwkeurigheid voor de detectie van diffuusglioom-infiltratie van de SUV en de TBR. Er was echter wel een significant verschil voor de SUV, maar niet voor de TBR, tussen tumor en normale samples. De diagnostische nauwkeurigheid van [^{18}F]FET TBR 60–90min was hoger dan die van [^{11}C]choline SUV 20–40min. We concluderen dat [^{18}F]FET PET nauwkeuriger is dan [^{11}C]choline PET voor de detectie van diffuusglioom-infiltratie.

In **hoofdstuk 9** presenteren we de resultaten van de directe vergelijking van de diagnostische nauwkeurigheid van meerdere MRI-sequenties, PET-tracers, en combinaties van MRI-sequentie(s) en/of PET-tracer(s), voor het detecteren van diffuus-glioom-infiltratie in 174 biopten van 20 patiënten. In aankleurende gliomen bleek de combinatie van ADC met [^{18}F]FET-PET de tumor beter te detecteren dan T1 met contrast-gewogen MRI en beter dan [^{18}F]FET-PET. In niet-aankleurende gliomen was geen enkele combinatie beter in het detecteren van de tumor dan standaard MRI. FLAIR-gewogen MRI was nauwkeuriger dan [^{18}F]FET-PET in niet-aankleurende gliomen. We construeerden een waarschijnlijkheidskaart voor de aanwezigheid van tumor, gebaseerd op de combinatie van ADC met [^{18}F]FET-PET, waarbij elke voxel de waarschijnlijkheid van tumoraanwezigheid representeerde op een schaal van 0 tot 100%. We concluderen

dat in aankleurende gliomen de combinatie van ADC met [^{18}F]FET-PET de mate van diffuusglioom-infiltratie beter detecteert dan standaard MRI en [^{18}F]FET-PET en dat dit kan leiden tot een betere lokale behandeling.

Hoofdstuk 10 beschrijft een onderzoek waarin we diffuusglioom-infiltratie met behulp van verschillende technieken kwantificeren en de intratumorale epigenetische heterogeniteit in 133 biopten van 16 patiënten bepalen. Diffuusglioom-infiltratie werd gekwantificeerd als de mate van tumorpuurheid door middel van (epi)genetische, histologische en radiologische karakteristieken. Een epigenetische maat (PAMES) correleerde het beste met alle andere maten. Tumorpuurheid vertoonde een hoge mate van variatie binnen patiënten. Intratumorale epigenetische heterogeniteit werd geanalyseerd door de moleculaire epigenetische classificatie van alle samples te bepalen. Deze classificatie werd vervolgens vergeleken met de tumorpuurheid. We concludeerden dat ruimtelijke heterogeniteit in de moleculaire epigenetische classificatie meestal verklaard kan worden door de variatie in tumorpuurheid en niet het gevolg is van biologische variatie. Genoomwijde analyse van intratumorale epigenetische heterogeniteit bevestigde deze bevindingen.

In **hoofdstuk 11** presenteren we ten slotte de algemene discussie over de volgende onderwerpen: huidige standaard beeldvorming voor het detecteren van diffuusglioom-infiltratie; combinaties van beeldvorming voor het detecteren van diffuusglioom-infiltratie; en kwantificatie van diffuusglioom-infiltratie. Tevens bediscussiëren we de toekomstperspectieven van een nieuw standaardprotocol voor beeldvorming van diffuse gliomen en lokale behandeling voorbij de afwijkingen op de huidige standaard-MRI. Op basis van deze discussie den we suggesties voor toekomstig onderzoek.

IV. List of publications

PUBLICATIONS INCLUDED IN THIS THESIS

Improved detection of diffuse glioma infiltration with imaging combinations: a diagnostic accuracy study.
Verburg N, Koopman T, Yaqub MM, Hoekstra OS, Lammertsma AA, Barkhof F, Pouwels PJW, Reijneveld JC, Heimans JJ, Rozemuller AJM, Bruynzeel AME, Lagerwaard F, Vandertop WP, Boellaard R, Wesseling P, de Witt Hamer PC.
Neuro Oncol. 2019 Sep 24. pii: noz180. doi: 10.1093/neuonc/noz180.

Direct comparison of [$_{11}$C] choline and [$_{18}$F] FET PET to detect glioma infiltration: a diagnostic accuracy study in eight patients.
Verburg N, Koopman T, Yaqub M, Hoekstra OS, Lammertsma AA, Schwarte LA, Barkhof F, Pouwels PJW, Heimans JJ, Reijneveld JC, Rozemuller AJM, Vandertop WP, Wesseling P, Boellaard R, de Witt Hamer PC.
EJNMMI Res. 2019 Jun 28;9(1):57. doi: 10.1186/s13550-019-0523-8.

Quantitative parametric maps of O-(2-[$_{18}$F]fluoroethyl)-L-tyrosine kinetics in diffuse glioma.
Koopman T, **Verburg N**, Pouwels PJ, Wesseling P, Hoekstra OS, De Witt Hamer PC, Lammertsma AA, Yaqub M, Boellaard R.
J Cereb Blood Flow Metab. 2019 May 24:271678X19851878. doi: 10.1177/0271678X19851878.

Quantification of O-(2-[$_{18}$F]fluoroethyl)-L-tyrosine kinetics in glioma.
Koopman T, **Verburg N**, Schuit RC, Pouwels PJW, Wesseling P, Windhorst AD, Hoekstra OS, de Witt Hamer PC, Lammertsma AA, Boellaard R, Yaqub M.
EJNMMI Res. 2018 Jul 31;8(1):72. doi: 10.1186/s13550-018-0418-0.

Diagnostic Accuracy of Neuroimaging to Delineate Diffuse Gliomas within the Brain: A Meta-Analysis.
Verburg N, Hoefnagels FWA, Barkhof F, Boellaard R, Goldman S, Guo J, Heimans JJ, Hoekstra OS, Jain R, Kinoshita M, Pouwels PJW, Price SJ, Reijneveld JC, Stadlbauer A, Vandertop WP, Wesseling P, Zwinderman AH, De Witt Hamer PC.
AJNR Am J Neuroradiol. 2017 Oct;38(10):1884-1891. doi: 10.3174/ajnr.A5368.

Accurate Delineation of Glioma Infiltration by Advanced PET/MR Neuro-Imaging (FRONTIER Study): A Diagnostic Study Protocol.
Verburg N, Pouwels PJ, Boellaard R, Barkhof F, Hoekstra OS, Reijneveld JC, Vandertop WP, Wesseling P, de Witt Hamer PC.
Neurosurgery. 2016 Oct;79(4):535-40. doi: 10.1227/NEU.0000000000001355.

In Vivo Accuracy of a Frameless Stereotactic Drilling Technique for Diagnostic Biopsies and Stereoelectroencephalography Depth Electrodes.
Verburg N, Baayen JC, Idema S, Klitsie MA, Claus S, de Jonge CS, Vandertop WP, de Witt Hamer PC.
World Neurosurg. 2016 Mar;87:392-8. doi: 10.1016/j.wneu.2015.11.041.

OTHER PUBLICATIONS

Quantitative Third Harmonic Generation Microscopy for Assessment of Glioma in Human Brain Tissue.
Zhang Z, de Munck JC, **Verburg N**, Rozemuller AJ, Vreuls W, Cakmak P, van Huizen LMG, Idema S, Aronica E, de Witt Hamer PC, Wesseling P, Groot ML.
Adv Sci (Weinh). 2019 Apr 5;6(11):1900163. doi: 10.1002/advs.201900163. eCollection 2019 Jun 5.

Inter-rater agreement in glioma segmentations on longitudinal MRI.
Visser M, Müller DMJ, van Duijn RJM, Smits M, **Verburg N**, Hendriks EJ, Nabuurs RJA, Bot JCJ, Eijgelaar RS, Witte M, van Herk MB, Barkhof F, de Witt Hamer PC, de Munck JC.
Neuroimage Clin. 2019;22:101727. doi: 10.1016/j.nicl.2019.101727.

Effects of physician-based emergency medical service dispatch in severe traumatic brain injury on prehospital run time.
Franschman G, **Verburg N**, Brens-Heldens V, Andriessen TM, Van der Naalt J, Peerdeman SM, Valk JP, Hoogerwerf N, Greuters S, Schober P, Vos PE, Christiaans HM, Boer C.
Injury. 2012 Nov;43(11):1838-42. doi: 10.1016/j.injury.2012.05.020.

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Name student: **N. Verburg**
PhD period: January 2016 – January 2020
PhD supervisors: prof. dr. W.P. Vandertop
prof. dr. P. Wesseling
prof. dr. P.C. de Witt Hamer

	Organizer	Year	EC
Mandatory			
Scientific integrity course	VUmc Academy	2018	2.0
Participation and presentation at international conferences	Society of Neuro Oncology	2016-2019	4.0
Participation and presentation at national conferences	Dutch Neuro Oncology workgroup meeting, Dutch Radiology Meeting, Dutch Neurosurgery Wintermeeting	2016-2019	4.0
Statistics course	Exemption		2.0
Oncology course	Exemption		3.0
Subtotal			**15.0**
Elective Mandatory			
Participation in weekly clinical oncology meetings	VUmc	2016-2019	2.0
Participation in weekly journal clubs	VUmc	2016-2019	4.0
Organization of journal clubs	VUmc	2016-2019	2.0
Tutor honors program student	VU	2016	2.0
Tutor student	VU	2019	2.0
Writing scientific articles under supervision	VUmc	2016-2019	2.0
Education for (scrub) nurses	Amstel Academy	2016-2018	2.0
Writing grant application	Niels Stensen Fellowship *Awarded*	2019	2.0
Subtotal			**18.0**
Elective			
Radiation hygiene	Boerhaave	2019	1.7
R2 introduction workshop	AMC Onco Genomics	2016	0.5
Subtotal			**2.2**
Total			**35.2**

VIII. List of dissertations Brain Tumor Center Amsterdam

Date	PhD Candidate	Thesis
10-06-2005	Carla Verstappen	Cancer therapy related neurotoxicity
28-09-2005	Maaike Vos	Evaluation of reponse, toxicity and outcome in glioma therapy
20-12-2005	Birgit Georger	Conditionally replicative adenoviruses for the treatment of malignant glioma and neuroblastoma
20-12-2005	Jacques Grill	Gene therapy and virotherapy of brain tumors with recombinant adenoviruses
19-06-2009	Fonnet Bleeker	Mutational profiling of glioblastoma
24-11-2009	Philip de Witt Hamer	Glioblastoma: between bed and bench
07-05-2010	Ingeborg Bosma	Cognitive dysfunction in glioma; underlying mechanisms and consequences
23-09-2010	Christian Badr	Bioluminescence imaging in glioblastom: monitoring of biological processes and novel therapeutics
08-11-2010	Linda Douw	Neural networks in brain tumors; the interplay between tumor, cognition, and epilepsy
10-06-2011	Sander Idema	Improving oncolytic viral therapy for glioma
05-10-2011	Anneke Niers	Novel biosensors for preclinical brain tumor analysis
16-11-2011	Krista van Nifterik	In vitro studies on radiation and temozolomide in human glioma
03-07-2012	Viola Caretti	Pioneering preclinical research in diffuse intrinsic pontine glioma: towards new treatment strategies
29-10-2012	Leonora Balaj	Exosomes: the biological messengers
08-02-2013	Marjolein de Groot	Epilepsy in brain tumor patients; towards improved and personalized treatment
04-06-2013	Edwin van Dellen	Lesions in the connected brain; a network perspective on brain tumors and lesional epilepsy
04-12-2013	Michiel Smits	Micro-RNA and epigenetic signaling in glioma angiogenesis
11-12-2013	Eefje Sizoo	The end-of-life phase of high-grade glioma patients; towards a dignified death
17-06-2014	Dannis van Vuurden	Innovative treatment targets in pediatric high-grade brain tumors

Date	PhD Candidate	Thesis
07-01-2015	Lotte Hiddingh	Treatment sensitizers for high-grade tumors
17-03-2015	Marc Jansen	Diffuse Intrinsic Pontine Glioma: clinical aspects and imaging
11-05-2015	Florien Boele	Towards improving health-related quality of life in glioma patients and their informal caregivers
30-09-2015	Johan Koekkoek	Epilepsy in glioma patients; optimizing treatment until the end of life
19-01-2016	Sjoerd van Rijn	Functional molecular imaging of cancer development and stem cell regeneration in the nervous system
24-03-2016	Hinke van Thuijl	Molecular characterization of low-grade glial neoplasms
18-05-2016	Avanita Prabowo	Molecular Features of long-term epilepsy-associated tumours; focus on glioneural tumours
08-06-2016	Ronald Willemse	Functional mapping of the sensorimotor cortex: clinical studies with MEG and fMRI
21-06-2016	Sharyar Mir	Novel treatment targets in high-grade brain tumors
01-07-2016	Femke Froklage	The role of the blood-brain barrier in drug-resistance and central neurotoxicity
03-11-2016	Thijs Crommentuijn	Development of vector-based strategies against glioblastoma
28-11-2017	Lot Sewing	Diffuse Intrinsic Pontine Glioma: disease models and translational research
28-11-2017	Sophie Veldhuijzen van Zanten	Diffuse Intrinsic Pontine Glioma: a multi-facetted and global view
22-12-2017	Remco Molenaar	Radiation in cancer. From cellular to clinical effects
23-01-2018	Tonny Lagerweij	Brain tumors: Preclinical imaging and novel therapies
14-09-2018	Ravi Narayan	Radiosensitizing and synergistic targeted therapy for glioblastoma
27-09-2018	Friso Hoefnagels	Imaging techniques as an adjunct in resective brain surgery
23-01-2020	Niels Verburg	Advanced imaging in glioma treatment; moving the frontier.

IX. Dankwoord

Ibiza, zomer 2018: “Sorry lief, maar ik moet nu even doorwerken want dan is het dit jaar nog allemaal klaar. Dat wil jij toch ook?” Dus… ruim een jaar en twee vakanties verder, waar helaas ook in gewerkt werd, is het nu dan écht zover. Wat begon met een idee over een onderzoekje naar fluorescerende middelen als coassistent heeft uiteindelijk geleid tot dit proefschrift aan het einde van mijn opleiding tot neurochirurg. Zoals iedereen weet is dit natuurlijk geen solo project en hebben er velen geholpen die ik graag wil bedanken.

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Mijn promotor, **prof. dr. W.P. Vandertop**. Beste professor, voor een promovendus met haast is bijna niet te beschrijven hoe prettig het was dat elk stuk binnen no-time, voorzien van zeer scherp en accuraat commentaar, terug kwam in mijn inbox. De precisie met betrekking tot de Nederlandse en Engelse taal heeft mij niet alleen geholpen in het schrijven van artikelen en beursaanvragen, maar ook nog eens met het behalen van het IELTS Engels examen. Dezelfde nauwkeurigheid is er op de OK en in het klinisch redeneren, waar ik enorm veel van heb geleerd. Daarnaast heb ik mij altijd gesteund gevoeld in het combineren van opleiding en promotie. Bedankt voor de flexibiliteit in het inzetten van mijn KWF beurs. Hopelijk kunnen we in de toekomst nog veel samenwerken. De (twee?)jaarlijkse assistenten BBQ’s ga ik missen!

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X. Curriculum Vitae

Niels Verburg was born on September 11, 1984 in Utrecht, The Netherlands. After obtaining his atheneum diploma at the St. Bonifatiuscollege in Utrecht in 2002, he worked as a volunteer in a primary school and hospital in Ghana, Africa. In 2003 he started to study Medicine at the Free University, Amsterdam. Between his study and internships he travelled to South and Central America. An internship in Emergency Medicine was followed at the Kalafong Hospital in Pretoria, South Africa. After graduating as a medical doctor in 2010, he started as a resident not in training at the department of Neurosurgery, VU Medical Center, Amsterdam. In 2012 his neurosurgical training commenced at the department of Neurosurgery, VU medical center, Amsterdam (chair: prof. dr. W.P. Vandertop) under guidance of prof. dr. S.M. Peerdeman. He trained for 6 months in spinal surgery under guidance of dr. G.J. Bouma at the OLVG West, Amsterdam. His training has completed in December 2019.

In 2011 he started his collaboration with prof. dr. P.C. de Witt Hamer, who just started a research group for diffuse glioma imaging. After receiving a grant of the Cancer Center Amsterdam in 2012, they initiated the FRONTIER study. In 2015, Niels obtained a Dutch Cancer Foundation Resident Grant, which allowed him to combine his residency with PhD research under guidance of prof. dr. P.C. de Witt Hamer, prof. dr. W.P. Vandertop and prof. dr. P. Wesseling. In 2017, he spent two months as a visiting scientist in the Computational Biology laboratory of prof. dr. R.J.W. Verhaak at the Jackson Laboratory for Genomic Medicine (Farmington, USA), which has led to an ongoing collaboration. The results of this collaboration and his PhD research are presented in this thesis. Recently he was awarded a Niels Stensen Fellowship that allows him to continue his research at the University of Cambridge, UK under guidance of dr. S.J. Price. Niels will be starting this new chapter in his life together with his wife Hannah and their two children Feline and Pepijn.